

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 July 2002 (04.07.2002)

PCT

(10) International Publication Number
WO 02/051258 A2

(51) International Patent Classification⁷: **A23G 3/30**

(21) International Application Number: **PCT/EP01/13473**

(22) International Filing Date:
19 December 2001 (19.12.2001)

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
MI2000A002810
22 December 2000 (22.12.2000) **IT**

(71) Applicant (for all designated States except US): **ATP
AVANT-GARDE TECHNOLOGIES PRODUCT
[CH/CH]; Marketing & Licensing SA, Via Pizzamiglio,
12, CH-6833 Vacallo (CH).**

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BADETTI, Rolando
[IT/IT]; Via Guerrazzi, 49, I-20052 Monza (IT).**

(74) Agent: **RICCARDI, Sergio; Via M. Melloni, 32, I-20129
Milano (IT).**

(81) Designated States (national): **AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
ZW.**

(84) Designated States (regional): **ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).**

Published:

— *without international search report and to be republished
upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: **A PROCESS FOR THE PREPARATION OF MEDICATED CHEWING GUMS CONTAINING ACTIVE PRINCIPLES
BEING LABILE TO THE HUMIDITY**

(57) Abstract: The invention concerns a process for the preparation of medicated chewing gums, containing active principles being labile to the humidity. Such a process is characterized in that the cold-ground gum is introduced in a mixer-dryer together to a dehydrated substance and rotatably placed under vacuum at a temperature comprised of 15-20°C.

WO 02/051258 A2

"A process for the preparation of medicated chewing gums containing active principles being labile to the humidity"

The present invention concerns a process for the preparation of medicated chewing gums, particularly a process for the preparation of base gum suitable as
5 component for medicated chewing gums containing active principles being labile to the humidity.

The base gum of chewing gums is a mixture comprising generally elastomers, resins, plasticizers, insoluble adjuvants, food antioxidants. All the base gums addressed to the preparation of chewing gums must be, of course, consistent with
10 the rules for the direct preparations for food use, and in the specific case of the medicated chewing gums, the problems generated for the presence of active principle must be taken into consideration.

For the production of the chewing gums there are two different approaches, the first one uses heat, while the second one consists of a cold-pressure technique of
15 powders. In such a case the base gum is therefore powdered and then mixed with one or more active principles, sweeteners, flavours and other various components in order to obtain an homogenous mixture. The obtained mixture is then passed through a tableting machine for the production of the tablets.

The base gum powder obtained in the grinding step before being mixed with
20 other components for the production of the finished gum is unloaded in suitable containers and let in the open air for variable times. In view of the fact that the grinding step occurred with a cold treatment and the ground gum comes out at a temperature below 0°C, the low temperature generates condensation of the humidity, present in the air, on the powder. The base gum slowly reaches the room
25 temperature and the final humidity level has a value comprised of 1-3%, which is variable in a range being dependent on how long the ground and cold gum is let in the open air and on the humidity level which is present in the particular moment.

Until now this final humidity level value in the gum can not be further lowered according to the known techniques, thereby the medicated gums containing active
30 principles being labile to the humidity are more difficult to be obtained. As a matter of fact a process for the production of chewing gums which are obtained by pressure and are comprised of active principles being labile to the humidity is not known.

It was surprisingly found that through a post-grinding treatment and a certain dwelling time of the base gum it is possible to reduce further the amount of the humidity of the base gum.

An object of the present invention is therefore to provide a process for the
5 preparation of the base gum which allows an active principle being labile to the humidity to be included in the final medicated gum.

The above indicated object is reached by providing the process as recited in claim 1. Further advantages of the invention are obtained through the characteristics recited in the dependent claims.

10 The process according to the present invention comprises the following steps:

- a) powdering the base gum in a grinding chamber;
- b) reducing the amount of the humidity of the ground gum,
- c) mixing the obtained powder with one or more active principles and suitable additives until the mixture is becoming homogeneous; and

15 d) pressing the obtained mixture in to tablets of desired size;
characterized in that in step b) the ground gum is introduced in a mixer-dryer together with a dehydrated substance and rotatably placed under vacuum at a temperature of 15-20°C.

According to the present invention the humidity level of the base gum of step
20 b) as measured with Karl Fischer apparatus is comprised between 0.01 and 0.1%.

The term "base gum" is intended as meaning a starting product of a mixture comprising generally elastomers, resins, plasticizers, insoluble adjuvants, food antioxidants.

Advantageously the dehydrated substance is anhydrous silica precipitate in
25 amount of 2% by weight.

According to an embodiment of the present invention the regulation of the temperature is carried out through circulation of a fluid in the cold jacket, preferably water and ethylene glycol at a temperature of 15-20°C.

Advantageously the dwelling time in the mixer-dryer is of 2-3 hours.

30 Preferably the active principles being labile to the humidity and mixed with the gum are selected from the group consisting of ascorbic acid, sodium ascorbate, acetylsalicylic acid, acetylcysteine.

Preferably the additives mixed with the gum are selected from the group

The mixing step c) is preferably carried out in a rotary powder mixer, selected between biconic mixer, "V" mixer or cubic mixer.

The so obtained mixture is preferably pressed with a rotary tableting machine which transforms into tablets of size of 8-28 mm.

5 Some illustrative embodiments now follow by way of not limitative example.

Example A

Preparation of base gum

The base gum, sold by GUM BASE S.p.A. of Lainate (Milano, Italy), is introduced in a loading hopper of a hammer mill, from which it is then passed to the grinding chamber. The cold-grinding is so carried out according to the prior art and at the outlet the ground base gum with granule sizes below 3mm is obtained.

The gum, at the outlet of the mill, is immediately sealed in a polythene bag in order to avoid the condensation of the room humidity. The gum is then introduced in a mixer-dryer together with 2% by weight of anhydrous silica precipitate. Vacuum is then carried out in the apparatus which is rotated.

A fluid (consisting of water and ethylene glycol), the temperature of which is regulated between 15 and 20°C, is contemporaneously circulated in the apparatus jacket.

The apparatus rotates and the ground gum is mixed with the silica; contemporaneously the gum takes heat from the fluid circulating in the apparatus jacket and the humidity possibly adsorbed during treatments is evaporated and taken away by the applied vacuum. After 2/3 hours of operation, the gum temperature reaches a value of 15-20°C; at this time the machine is stopped, the gum is unloading in to double polythene bag and placed in a cardboard container. Between the two bags a sachet containing silica gel as dehydrating substance, is introduced.

The so obtained humidity level in the gum is comprised between 0.01-0.1% as measured with Karl Fischer apparatus.

Example n.1

In a "biconical" mixer the following powders are introduced:

30	Base gum ground and obtained in Example A	mg 1050	Gum
	Ascorbic acid	mg 206	Active Principle
	Sodium ascorbate	mg 331	Active Principle
	Aspartame	mg 7	Sweetener

	Sorbitol	mg	150	Sweetener
	Isomalt	mg	41	Sweetener
	Anhydrous Silica Precipitate	mg	40	antiadherent
	Talc	mg	40	antiadherent
5	Magnesium Stearate	mg	30	Lubricant
	Powdered Orange flavour	mg	60	Flavourant
	Powdered Tangerine Flavour	mg	40	Flavourant

mg 2000

10 All the above ingredients are mixed for 20 minutes and the obtained powder is pressed with a tableting machine obtaining gums of 2 g. The humidity of the tablets just produced and measured with the Karl Fischer apparatus is 0.22%. Such a result allowed a product which is stable for two years to be obtained.

Example n.2

15 In a "biconical" mixer the following powders are introduced:

	Base gum ground and obtained in Example A	mg	1065	Gum
	Coated Salicic acid	mg	516	Active Principle
	Aspartame	mg	6	Sweetener
	Potassium Acesulphame	mg	4	Sweetener
20	Betacyclodextrin	mg	74	Sweetener
	Silica Precipitate	mg	40	antiadherent
	Talc	mg	40	antiadherent
	Powdered Spearmint Flavour	mg	50	Flavourant
	Ammonium glycyrrhizate	mg	5	Flavourant

25 mg 1800

All the above ingredients are mixed for 20 minutes and the obtained powder is pressed with a tableting machine obtaining gums of 1.8 g.

30 The humidity of the tablets just produced and measured with the Karl Fischer apparatus is 0.11%. Such a result allowed a product which is stable for two years to be obtained.

Example n.3

	Base gum ground and obtained in Example A	mg 690	Gum
	Acetyl cysteine	mg 100	Active Principle
	Aspartame	mg 3	Sweetener
	Potassium Acesulphame	mg 2	Sweetener
5	Betacyclodextrin	mg 130	Audiuvant
	Anhydrous Silica Precipitate	mg 35	antiadherent
	Talc	mg 35	antiadherent
	Powdered Orange flavour	mg 100	Flavourant
	Ammonium glycirinizate	mg 5	Flavourant
10	Magnesium stearate	mg 30	Lubrificant
	Xilitol	mg 70	Sweetener

mg 1200

15 All the above ingredients are mixed for 20 minutes and the obtained powder is pressed with a tableting machine obtaining gums of 1.2 g. The humidity of the tablets just produced and measured with the Karl Fischer apparatus is 0.19%. Such a result allowed a product which is stable for two years to be obtained

CLAIMS

1. A process for the preparation of medicated gums comprising the step of:
 - a) making in powder form the base gum in a grinding chamber;
 - b) reducing the amount of humidity of the ground gum;
 - 5 c) mixing the obtained powder with one or more active principles and suitable additives in order to obtain a homogenous mixture; and
 - d) pressing the obtained mixer in to tablets of desired sizes,characterized in that in step b) the ground gum is introduced in a mixer-dryer together with a dehydrated substance and rotatably placed under vacuum at a
10 temperature of 15-20°C.
2. The process according to claim 1 wherein the humidity level of the base gum obtained by step b) as measured with Karl Fischer apparatus is comprised of 0.01-0.1%.
3. The process according to claim 1 or 2 wherein the dehydrated substance is
15 anhydrous silica precipitate.
4. The process according to anyone of the preceding claims wherein the dehydrated substance is anhydrous silica precipitate in amount of 2% by weight.
5. The process according to anyone of the preceding claims wherein the regulation of the temperature is carried out through circulation in the cold jacket of a fluid at a
20 temperature of 15-20°C.
6. The process according to claim 5 wherein the fluid is ethylene glycol and water.
7. The process according to anyone of the preceding claims wherein the dwelling time in the mixer-dryer is of 2-3 hours.
8. The process according to anyone of the preceding claims wherein the active
25 principles mixed with the gum are selected from the group consisting of ascorbic acid, sodium ascorbate, acetylsalicylic acid, acetylcysteine.
9. The process according to anyone of the preceding claims wherein the additives mixed with gum are selected from the group consisting of sweeteners, flavours, lubricants, antiadherents, fillers.
- 30 10. The processing according to anyone of the preceding claims wherein the mixing step b) is carried out in a rotary powder mixer, preferably selected between biconic mixer, "V" mixer or cubic mixer and the pressuring step c) is carried out in a rotary tableting machine.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 July 2002 (04.07.2002)

PCT

(10) International Publication Number
WO 02/051258 A3

(51) International Patent Classification⁷: A23G 3/30, A61K 9/68

(21) International Application Number: PCT/EP01/13473

(22) International Filing Date:
19 December 2001 (19.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2000A002810
22 December 2000 (22.12.2000) IT

(71) Applicant (*for all designated States except US*): ATP
AVANT-GARDE TECHNOLOGIES PRODUCT
[CH/CH]; Marketing & Licensing SA, Via Pizzamiglio,
12, CH-6833 Vacallo (CH).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): BADETTI, Rolando
[IT/IT]; Via Guerrazzi, 49, I-20052 Monza (IT).

(74) Agent: RICCARDI, Sergio; Via M. Melloni, 32, I-20129
Milano (IT).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
20 March 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A PROCESS FOR THE PREPARATION OF MEDICATED CHEWING GUMS CONTAINING ACTIVE PRINCIPLES BEING LABILE TO THE HUMIDITY

(57) Abstract: The invention concerns a process for the preparation of medicated chewing gums, containing active principles being labile to the humidity. Such a process is characterized in that the cold-ground gum is introduced in a mixer-dryer together to a dehydrated substance and rotatably placed under vacuum at a temperature comprised of 15-20°C.



WO 02/051258 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/13473

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A2363/30 A61K9/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A23G A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4'737 366 A (GERGELY GERHARD ET AL) 12 April 1988 (1988-04-12) column 1, line 52 - column 2, line 9 column 2, line 49 - line 58 column 3; example 1 ---	1
A	US 4 514 422 A (YANG ROBERT ET AL) 30 April 1985 (1985-04-30) column 1, line 7 - line 10 column 2, line 51 - line 54 column 5, line 12 - line 15 column 5, line 46 - line 61 claim 1 ---	1
A	EP 0 407 019 A (WARNER LAMBERT CO) 9 January 1991 (1991-01-09) page 4, line 48 - page 5, line 12 page 17, line 25 - line 30 ---	1, 3, 4
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

13 December 2002

Date of mailing of the international search report

23/12/2002

Name and mailing address of the ISA
 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

VON EGGELKRAUT, S

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 01/13473

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 150 161 A (RUDOLPH MARVIN J ET AL) 17 April 1979 (1979-04-17) column 3, line 67 -column 4, line 11 column 5, line 17 - line 29 claim 1 -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/13473

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4737366	A	12-04-1988	AT 55244 T	15-08-1990
			AU 5356586 A	29-07-1986
			DE 3579170 D1	13-09-1990
			WO 8603967 A1	17-07-1986
			EP 0235159 A1	09-09-1987
			FI 872731 A ,B,	18-06-1987
			JP 7096496 B	18-10-1995
			JP 62501419 T	11-06-1987
US 4514422	A	30-04-1985	AR 231054 A1	28-09-1984
			AU 548651 B2	19-12-1985
			AU 9165582 A	30-06-1983
			CA 1205666 A1	10-06-1986
			DE 3280375 D1	19-12-1991
			EP 0082670 A2	29-06-1983
			ES 8405249 A1	16-09-1984
			HK 115094 A	27-10-1994
			JP 1395594 C	24-08-1987
			JP 58129935 A	03-08-1983
			JP 61056981 B	04-12-1986
			ZA 8208876 A	30-11-1983
EP 0407019	A	09-01-1991	US 4980178 A	25-12-1990
			US 4980177 A	25-12-1990
			AU 5874990 A	10-01-1991
			CA 2020620 A1	08-01-1991
			CN 1048486 A	16-01-1991
			DE 69026540 D1	23-05-1996
			DE 69026540 T2	14-11-1996
			EP 0407019 A2	09-01-1991
			ES 2085332 T3	01-06-1996
			GR 3019977 T3	31-08-1996
			IE 902474 A1	13-02-1991
			JP 3119961 A	22-05-1991
			JP 3224809 B2	05-11-2001
			NO 903022 A	08-01-1991
			ZA 9005332 A	25-03-1992
			PT 94613 A	20-03-1991
US 4150161	A	17-04-1979	BE 864853 A1	14-09-1978
			CA 1107125 A1	18-08-1981
			CH 631325 A5	13-08-1982
			DE 2811168 A1	28-09-1978
			ES 467857 A1	01-09-1979
			FR 2383611 A1	13-10-1978
			GB 1567743 A	21-05-1980
			HK 69480 A	19-12-1980
			IE 46444 B1	15-06-1983
			IT 1155885 B	28-01-1987
			LU 79237 A1	28-06-1978
			NL 7802811 A	19-09-1978
			SE 436538 B	07-01-1985
			SE 7802924 A	16-09-1978